

SUPPORT FOR THE AMENDMENT

Support for the amendment to claim 1 is found in claim 1 as originally presented. No new matter would be added to this application by entry of this amendment. Support for claim 8 is found on page 1, lines 4-12 of the specification.

Upon entry of this amendment, claims 1-8 will now be active in this application.

REQUEST FOR RECONSIDERATION

The claimed invention is directed to a method for producing alkyl (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate by epimeric separation by liquid chromatography treatment using silica gel as the packing material.

During the preparation of optically active pharmaceuticals, it is often necessary to either 1) conduct optical resolution of a racemic mixture and purification by recrystallization, in which case half of the original material is wasted or 2) conduct entantioselective synthesis in which purification by recrystallization cannot be carried out and epimers can not be removed. (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate is a useful intermediate for the production of pharmaceuticals and which can be used for the production of a cholesterol-reducing agent. Therefore efficient methods for producing (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate are sought.

Applicants have discovered that epimeric separation using silica gel as the packing material may be effectively conducted in a simple, cost-effective method which does not waste the less-useful antipode. Such a method is nowhere disclosed or suggested in the cited prior art of record.

The rejections of claims 1-5 and 7 under 35 U.S.C. §102(a) and (b) and of claim 6 under 35 U.S.C. §103(a) over Ikeda et al., U.S. 5,939,552, Nagamatsu et al. (1999), Chen et al., U.S. 6,835,838 and Onishi et al., U.S. 6,946,557 are respectfully traversed.

None of the cited references discloses or suggests a method for producing the claimed compound by 1) separation of epimers or 2) by using silica gel as the packing material in a liquid chromatography.

Ikeda et al. describes **optical resolution** of a racemic mixture of an optically active mevalonolactone compound by means of a batch system chromatography which uses a column filled with a filler selected from a group consisting of particles of polysaccharide ester derivative, particles of a polysaccharide carbamate derivative and particles of a support which carries a polysaccharide ester derivative and/or a polysaccharide carbamate derivative (column 1, lines 51-58).

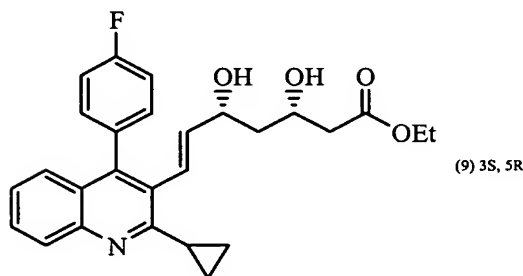
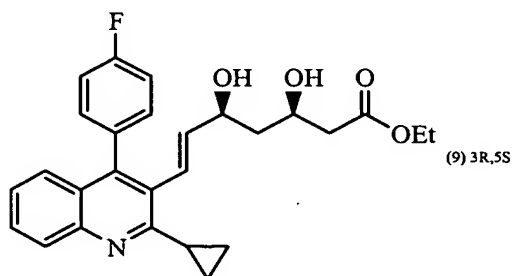
None of these chromatography supports are silica gel packing material. To the contrary, the packing material is a polysaccharide ester derivative and/or polysaccharide carbamate derivative. While the Examiner notes the description of silica gel at column 6, line 30, this recitation is as an inorganic support for the polysaccharide ester derivative or polysaccharide carbamate derivative and therefore the packing material is not a silica gel.

In contrast, the claimed invention is directed to a method in which silica gel as the packing material is used in liquid chromatography to separate epimers. As the cited reference fails to disclose or suggest using silica gel as the packing material in a liquid chromatography treatment, the claimed invention is clearly neither anticipated nor rendered obvious by this reference and accordingly withdrawal of the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103(a) is respectfully requested.

Furthermore, Ikeda et al., fail to describe the separation of an epimeric mixture of compounds as claimed. As previously noted, the reference describes “conducting optical

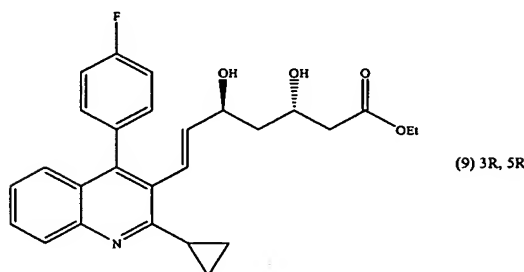
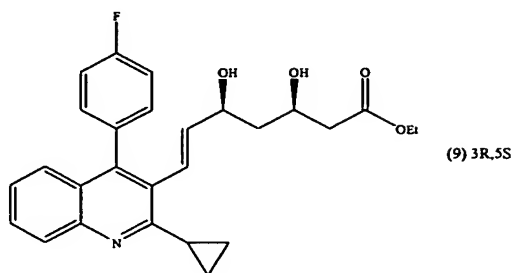
resolution of the racemic mixture of an optically active mevalonolactone compound...”

(column 1, lines 49-53). Optical resolution of a racemic mixture of optically active enantiomeric mevalonolactone compounds describes the separation of compounds which are identical but for the absolute stereochemistry. In other words, the relative stereochemistry throughout the molecule is the same. As to the compound of formula (9) identified on column 4 of the reference, the two enantiomers are as follows:



With this pair of enantiomers, the relative stereochemistry between the two compounds is the same and only the absolute stereochemistry differs.

In contrast, epimeric separation involves separation of compounds which differ in relative to stereochemistry, a process which is not suggested by optical resolution. Epimers of the compound of formula (9) of Ikeda et al. are as follows:



In pair of epimers, the relative stereochemistry the two compounds is different. The corresponding pair of enantiomers is not depicted. When a compound is optically resolved, one half of the material is wasted as having the wrong absolute configuration. Thus, Ikeda et al. is directed to a fundamentally different process in which resolution of optically active enantiomers is conducted while the claimed invention is directed to the separation of epimeric compounds.

Likewise, Nagamatsu et al. fail to disclose or suggest a method in which epimers are separates using silica gel as the packing material in a liquid chromatography treatment. The reference describes separation of DOLE **racemic mixture** on slightly modified Chiralcel OF, 20 μ m (Daicel) (page 58, section 2.5. Columns). The use of Chiralcel OF is not the use of silica gel as the packing material. Chiralcel OF is cellulose tris (4-chlorophenyl carbamate **coated on** a silica gel substrate. (see attached printout from Daicel Chemical Industries website). As a coated silica gel substrate, Chiralcel OF is not silica gel as the packing material, but rather is silica gel used as a support for cellulose tris (4-chlorophenyl carbamate). The cellulose derivative is the packing material for this process and not silica gel. As the reference fails to disclose or suggest the use of **silica gel as the packing material**

in a liquid chromatography treatment, the claimed invention is clearly neither anticipated nor rendered obvious by this reference.

Moreover, Nagamatsu et al. describe the separation of a DOLE racemic mixture not separation of epimers and accordingly does not suggest the claimed process.

Chen et al. at column 16, describe the use of Chiralpak AD in order to evaluate the optical purity of pitavastatin calcium. The use of Chiralpak AD is not the use silica gel as a packing material in a liquid chromatography treatment. Chiralpak AD is amylose tris (3,5-dimethylphenyl carbamate) coated on a silica-gel substrate (see attached from Diacel Chemical Industries website). As such, Chiralpak AD is not a silica gel but is rather a modified silica gel in which the resolving support is amylose tris (3,5-dimethylphenyl carbamate).

Moreover, Example 5 of Chen et al. identified by the examiner fails to disclose epimeric separation but rather describes separation of **enantiomers** and accordingly would not make obvious the claimed invention in which epimers are separated.

Onishi et al. describe the use of cellulose tris (4-chlorophenyl carbamate) supported on a carrier as a filler for liquid chromatography. Cellulose tris (4-chlorophenyl carbamate) is Chiralcel OF, and as discussed above is not the use of silica gel as the packing material. Again the silica gel is merely a support for the cellulose derivative such that the use of a silica support is not the use of silica gel as the packing material in the liquid chromatography treatment. Accordingly, the claims are neither anticipated nor rendered obvious from this disclosure and accordingly withdrawal of the rejections under 35 U.S.C. §102(a) and (b) and 35 U.S.C. §103(a) are respectfully requested.

Since none of the references disclose or suggest using silica gel as the packing material in a liquid chromatography treatment nor the separation of epimers in which the relative stereochemistry of the only two optically active centers differ, the claimed invention

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is clearly neither anticipated nor rendered obvious from this reference. Accordingly
withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

Applicants submit this application is now in condition for allowance and early
notification of such action is earnestly solicited.

Respectfully submitted,

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